CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125293

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

July 29, 2010

BLA #: STN 125293
PRODUCT NAME: Krystexxa (PEGloticase)

SUBMISSION DATE: March 15, 2010
MIDCYCLE: June 15, 2010
PDUFA GOAL DATE: September 15, 2010

FROM: Howard Anderson, PhD, Biologist 18 Aug 2010

THROUGH: Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry.
Richard Ledwidge, PhD, Chemist 8/18/10
Gibbes Johnson, PhD, Chief Laboratory of Chemistry
Barry Cherney, PhD, Deputy Directory Division of Therapeutic Proteins 8-18-10

SUBJECT: Product Quality Review of BLA 125293 Complete Response (July 31, 2009 FDA CR Letter to Savient)

INDICATION: Treatment Resistant Gout

ROUTE OF ADMIN: Oral

SPONSOR: Savient Pharmaceuticals, INC
One Tower Center, 14th Floor
East Brunswick, NJ 08816

CLINICAL DIVISION: Division of Pulmonary, Allergy, and Rheumatology Products

RPM: Ramani Sista (301-796-1236)

RECOMMENDATION: The major issue resulting in a recommendation to not approve the original application centered on the fact that the sponsor made a major change to the manufacturing process after the phase III clinical trial. This change resulted in a to-be-marketed product that was not physico-chemically comparable (b) (4) to the product used in the phase III clinical trial. The sponsor has changed the manufacturing process back to the process

used to produce the phase III clinical trial material. The original application also had deficiencies with the QC release and stability testing program. These issues have now largely been addressed. Outstanding issues with the testing program still exist, but can be addressed as post-marketing commitments. They are provided in the next section of this review. In summary, Savient has adequately addressed all the issues communicated in the CR letter and has greatly improved the product quality of Krystexxa. I therefore recommend approval of BLA STN 125293.

Post Marketing Commitments

1) To revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. The new acceptance criteria for the assay will be submitted in a supplement to the license by **[Insert Date].**

2) To conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over and under pegylated uricase molecules. The results of the study will be provided by **[Insert Date]**.

3) To re-evaluate the release and stability acceptance criteria for the following assays;
    a. enzymatic activity
    b. K_m and k_{cat} determination by product accumulation and substrate depletion
    c. monomer and HMW forms by SEC-HPLC Abs_{220}
    d. monomer HMW and LMW forms by Abs_{220}

    The acceptance criteria for the drug substance and drug product will be reevaluated and after **[Inset Number]** lots are manufactured and the revised specifications submitted in a supplement to the license by **[Insert Date]**.

4) To develop and implement an enzymatic assay, based on a measure of product accumulation, that determines K_m and k_{cat} values for release of uricase intermediate. The new specification and supporting data will be submitted in a supplement to the license by **[Insert Date]**.

5) To include stress conditions in the annual stability program for drug substance and drug product. The revised stability protocols will be submitted by in a supplement to the license by **[Insert Date]**.

6) To evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250mL saline solution (pH 4.5) has on the final pH of the infusion solution. The results of the study and risk mitigation strategies, if the final pH is below 6.2, will be submitted by **[Insert Date]**.

7) To provide the results of studies supporting the proposed drug product overfill. A report containing the result of studies and justification will be provided by **[Insert Date]**.

Summary

The Krystexxa BLA original submission occurred on October 31, 2008, and was designated to be a six month priority review. The PUDFA action date was extended three months due to the submission of a major clinical amendment during the review cycle. Dr. Anderson was responsible for review of the Drug Substance and Dr. Richard Ledwidge was responsible for the review of the Drug Product in the Product Quality Section of the BLA. Dr. Lacana participated as the Team Leader for the initial review.

The original BLA was found to contain product quality deficiencies and on July 31, 2009, a Complete Response (CR) letter was sent to Savient Pharmaceuticals. It contained 19 product quality items. The first 11 were generated by DTP (Division of Therapeutic Proteins), and items 11 to 19 were generated by Drs. Farbman and Hughes of the Biotech Manufacturing Team of DMPQ/OC/CDER.

After review of the initial application DTP could not recommend approval of the application primarily due to the fact that a major manufacturing process change occurred after the phase III clinical trial **(Process A)**. Only a single lot of material was evaluated for safety and efficacy in the phase III trial. This lot was manufactured with a (b) (4) This resulted in 9 molecules of PEG per uricase monomer. The data provided in the BLA indicated that the products manufactured using the two processes were not physico-chemically comparable. This topic is covered in detail in the original reviews. DTP concluded that (b) (4) of this product is a critical quality attribute for Krystexxa (b) (4) It should be noted that other deficiencies were communicated to the sponsor in the CR letter and concerned the QC release and stability testing program.

A Type A meeting was conducted on September 14, 2009, in which FDA and Savient discussed and agreed upon a strategy to address the 19 product quality CR issues. Savient indicated that their strategy to address the PEGylation step in the manufacturing process would be to revert to the conditions used to manufacture the phase III clinical trial material. This manufacturing process is referred to as **Process C** in the BLA. FDA agreed with this strategy as well as a plan for Savient to address technical aspects to improve the quality release and stability testing program.

This complete response primary review was performed by Dr. Anderson. In summary, the sponsor has largely addressed all deficiencies using the strategy agreed upon with the FDA, and provided adequate information in this CR. The Krystexxa manufactured by

process C [redacted] (b) (4) is physico-chemically comparable to Krystexxa used in the phase III clinical trial. The lot release testing program has been improved, and the updated specifications for the uricase intermediate, drug substance and drug product can be found in the appendix section of this review.

Real time stability data have been updated and include 3 years for the single clinical lot (5682003100, obtained with Process A). For process B, 2.5 years for 4 lots, 2 years for 1 lot, 1.5 years for 3 lots of stability data are provided. For process C, 6 months for 3 lots of stability data are provided. A summary of all stability lots can be found in the appendix of this review as well as the Krystexxa stability protocol. **These data support the proposed two year expiry for Krystexxa** since only minor excursions occurred outside the acceptance ranges for some of the lots, and no trends were observed to indicate that the product in unstable at the proposed storage condition of [redacted] (b) (4)

[redacted] (b) (4)

23 Page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From:	**Emanuela Lacana, Ph.D.** **Division of Therapeutic Proteins (DTP)**
Through:	**Barry Cherney, Ph.D** **Deputy Director** **Division of Therapeutic Proteins (DTP)**
	Amy Rosenberg, MD **Director** **Division of Therapeutic Proteins (DTP)**
BLA Number:	**125293**
Product:	**KRYSTEXXA (pegloticase for injection)**
Sponsor:	**Savient Pharmaceuticals**
Date of Review:	**July 23, 2010**
Date of CDTL Memo:	**August 5, 2010**

This memo does not follow the OBP template. It is a summary of the evaluation of the sponsor's responses to the complete response letter issued July 29, 2009.

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does recommend approval of BLA125293 for KRYSTEXXA manufactured by Savient Pharmaceutical Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of KRYSTEXXA is well controlled, and leads to a product that is pure and potent. The sponsor has addressed all the CMC issues that were communicated in the complete response letter dated July 29, 2009, and the DTP conclusion is that the issues have been adequately addressed. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture pegloticase drug substance at Bio-Technology General (Israel) Ltd. (BTG). The final formulated product will be manufactured, filled, labeled, and packaged at Enzon Pharmaceuticals, Inc. (6925 Guion Road, Indianapolis, IN 46268). You may label your product with the proprietary name KRYSTEXXA and will market it in vials containing (b) (4) of pegloticase corresponding to8 mg uricase protein conjugated to 24 mg of 10 kDa mPEG.

The dating period for KRYSTEXXA shall be 24 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date (b) (4) of the formulated drug product. The dating period for your drug substance shall be 6 months when stored at 2 to 8 °C. The dating period for the uricase intermediate shall be 54 days when stored at 2 to 8 °C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including results of stability studies from the first three production lots. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of pegloticase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Alglucosidase alfa, or in the manufacturing facilities.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

1) To revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. The new acceptance criteria for the assay will be submitted in a supplement to the license by **[Insert Date].**

2) To conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over and under pegylated uricase molecules. The results of the study will be provided by **[Insert Date]**.

3) To re-evaluate the release and stability acceptance criteria for the following assays;
   a. enzymatic activity
   b. K_m and k_{cat} determination by product accumulation and substrate depletion
   c. monomer and HMW forms by SEC-HPLC Abs_{220}
   d. monomer HMW and LMW forms by Abs_{220}

   The acceptance criteria for the drug substance and drug product will be reevaluated and after **[Inset Number]** lots are manufactured and the revised specifications submitted in a supplement to the license by **[Insert Date]**.

4) To develop and implement an enzymatic assay, based on a measure of product accumulation, that determines K_m and k_{cat} values for release of uricase intermediate. The new specification and supporting data will be submitted in a supplement to the license by **[Insert Date]**.

5) To include stress conditions in the annual stability program for drug substance and drug product. The revised stability protocols will be submitted by in a supplement to the license by **[Insert Date]**.

6) To evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250mL saline solution (pH 4.5) has on the final pH of the infusion solution. The results of the study and risk mitigation strategies, if the final pH is below 6.2, will be submitted by **[Insert Date]**.

7) To provide the results of studies supporting the proposed drug product overfill. A report containing the result of studies and justification will be provided by **[Insert Date]**.

IV. EXECUTIVE SUMMARY

The submission received March 15, 2010, constitute a complete response to the CR letter issued to Savient Pharmaceuticals on July 29, 2009. The issues conveyed to the sponsor are summarized below:

Comparability

(b) (4)

[redacted]

Drug substance and drug product release testing

Savient was asked to enhance the quality strategy program for drug substance and drug product. The following issues were raised by DTP

1. Introduction of an assay to monitor lysine site occupancy;
2. Tighten acceptance criteria;
3. Include an assay to monitor for drug substance and product degradation;
4. Include an identity assay;
5. Include an assay to measure (b) (4)

In regard to the lysine occupancy the sponsor has developed a peptide mapping-based assay. The assay is adequate to monitor lysine occupancy by PEG molecules, but the acceptance criteria for the assay should be revised. The sponsor monitors loss of PEGylated peptides, but we recommended that acceptance criteria also be established for representative non-PEGylated peptides. These issues can be addressed as PMC.

2 Page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy Rosenberg, MD Director Division of Therapeutic Proteins Barry Cherney, Ph.D Deputy Director Division of Therapeutic Proteins	Barry Cherney 8-18-10
Gibbes Johnson, Ph.D Laboratory Chief, Laboratory of Chemistry, Division of Therapeutic Proteins Emanuela Lacana, Ph.D Associate Laboratory Chief, Laboratory of Chemistry, Division of Therapeutic Proteins	8-17-10 Emanuela Lacana 13 August, 2010
Howard Anderson, Ph.D, Division of Therapeutic Proteins Richard Ledwidge, Ph.D Division of Therapeutic Proteins	18 Aug 2010 8/17/10

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

TO: The File STN 125293
FROM: Emanuela Lacana, Ph.D., Acting Associate Lab Chief, DTP/OBP/OPS/CDER
THROUGH: Gibbes Johnson, Ph.D., Chief Lab. of Chemistry
Barry Cherney, Ph.D., Deputy Director DTP
Amy Rosenberg, M.D., Ph.D, Division Director

7-22-09
7-22-09

SUBJECT: Executive Summary of STN 125293 Original Submission
Pegylated Modified Porcine Uricase

CDER RECEIPT DATE: 31 October 2008
MID CYCLE DATE: 31 January 2009
PUDFA DATE: 31 April 2009
PUDFA DATE EXTENSION: 31 July 2009

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of BLA125293 for Pegloticase manufactured by Savient Pharmaceuticals, Inc. The issue with approvability relates to the comparability of the product used in the Phase III clinical trial and the material produced for commercial production. A change in the manufacturing process has resulted in Phase III clinical material with a (b) (4) than the proposed commercial material and (b) (4) than the proposed commercial product (9 PEG/molecule). The potential impact on safety and efficacy of this change is unknown since the pivotal clinical experience was restricted to use of only one lot of phase III drug product characterized by the (b) (4). Thus, from a product quality assessment, the Division cannot conclude that the commercial product is comparable to the proposed commercial product based on quality criteria. Whether the commercial material will have a similar clinical profile with regard to safety and efficacy as the phase III material is not known and would require non-clinical and/or clinical data in order to support a determination of product comparability. It should be noted that the product used in phase 2 is comparable by quality criteria to the commercial material and thus it might be possible to leverage clinical data from the phase 2 studies in addressing our concerns

9 Page(s) Withheld in Full immediately following this page as B4 (CCI/TS)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

July 17, 2009

TO: The File STN 125293
FROM: Howard Anderson, Ph.D., Biologist, DTP/OBP/OPS/CDER 7-17-09
THROUGH: Emanuela Lacana, Ph.D., Associate Chief Lab. of Chemistry 7/17/09
Gibbes Johnson, Ph.D., Chief Lab. of Chemistry
Barry Cherney, Ph.D., Deputy Director DTP 7-17-09
Amy Rosenberg, M.D., Ph.D, Division Director

SUBJECT: Quality Review of STN 125293 Drug Substance, Original Submission Pegylated Modified Porcine Uricase

CDER RECEIPT DATE: 31 October 2008
MID CYCLE DATE: 31 January 2009
PUDFA DATE: 31 April 2009
PUDFA DATE EXTENSION: 31 July 2009

SPONSOR: Savient Pharmaceuticals, Inc. (Savient)
One Tower Center, 14th Floor
East Brunswick, NJ 00816

DRUG SUBSTANCE MANUFACTURER: Bio-Technology General (Israel) Ltd.
Be'er Tivia Industrial Zone
P.O. Box 571
Kiryat Malachi 83104
ISRAEL

DRUG PRODUCT: Reviewed by Richard Ledwidge, Ph.D, Biologist, DTP

INDICATION: Treatment Resistant Gout
CLINICAL BRANCH: Division of Anesthesia, Analgesia and Rheumatology Products
RPM: Diana Walker, Ph.D

DMF LOA Provided: (b) (4)

ADMINISTRATIVE:

This application involves puricase, a clear colorless, sterile solution containing 8 mg/ml of uricase protein conjugated to methoxypolyethylene glycol (mPEG) in phosphate buffered saline. Savient has requested a categorical exclusion from an environmental assessment. The expected introduction concentration of the active moiety into the aquatic environment will be (b) (4) Under 21 CFR Section 25.31(b) Puricase meets the criteria for a categorical exclusion regarding an action on this BLA since the active moiety estimated concentration at the point of entry into the aquatic environment will be below 1 part per billion. I therefore recommend approval of this request.

The drug substance section of this review was written by Howard Anderson. During the review deficiencies were identified that required additional information from the sponsor. An information request was sent to the sponsor on May 28, 2009. The sponsor provided responses in a letter dated June 11, 2009. The sponsors response have been included in this review.

RECOMMENDATION: Complete Response

The following issues need to be addressed by Savient for complete review of the CMC section of the BLA. Provided below are issues identified during the primary drug substance quality review. The issues are grouped by significance. Item number 1 is critical and needs to be addressed for my recommendation to approve the application. The additional items would have been addressed as post marketing commitments if the recommendation was for approval, but will now be included in the Complete Response letter.

Complete Response Issues (Finalized CR comments are included in the Executive Summary)

1. The manufacturing process for the phase III material has been significantly changed to produce validation and marketing lots. (b) (4) The comparability study "Analysis and comparison of the Phase III Clinical Trial Puricase with the Puricase Manufactured by the Commercial Process" results indicated the two molecules are not physicochemical comparable and are structurally different. Therefore the molecules need to be evaluated clinically to determine the significance of physiochemical differences.

2. Savient should update their drug substance and drug product release testing program, as follows:

i. Include peptide mapping to assess lysine site occupancy and develop acceptance criteria for the lysine most frequently occupied.
ii. Tighten acceptance criteria to reflect manufacturing history, process capability and clinical experience for K_m, k_{cat}, (b) (4)
iii. Include an assay that monitors product-related impurities and product degradation.
iv. Include an identity test that allows for the determination of the primary sequence of the product.
v. Re-instate process-related impurities tests that were removed from the release testing program (b) (4)

3 Savient should update their uricase intermediate release and testing program, as follows:

vi. (b) (4)
vii. Include an identity test that allows for the determination of the primary sequence of the uricase intermediate.

4 Savient should update the uricase intermediate reference standard testing to include measurement of potency by specific activity and K_m and k_{cat} and develop acceptance criteria for these tests.

5 Savient should update their drug substance and drug product stability testing program, as follows:

i. Provide updated acceptance criteria that reflect manufacturing history, process capability and clinical experience for K_m, k_{cat}, (b) (4)
ii. Include an assay that monitors product-related impurities and product degradation.
iii. Include an identity test that allows for the determination of the primary sequence of the product.

6 Savient should provide studies addressing the effect of leachable/extractable on product quality, for both drug substance and uricase intermediate.

7 Savient should implement a system suitability control for the SDS-PAGE assay and establish quantitative acceptance criteria.

8 Savient should increase accuracy for the ELISA quantification of (b) (4) in drug substance testing.

9 Savient should validate the accuracy of SEC-HPLC for high molecular weight species.

10 Savient should revise the limit for periodic testing of the cell banks (b) (4) to reflect historical trends.

11 Savient should provide characterization data on the (b) (4)

12 Savient should develop a robust qualification protocol for reference standard with acceptance criteria/limits for all assays used in the protocol.

13 Savient should provide additional validation data to support the suitability of the antibody used to detect host cell proteins.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

July 17, 2009

TO: The File STN 125293
FROM: Richard Ledwidge, Ph.D., Chemist, DTP/OBP/OPS/CDER 7/17/09
THROUGH: Emanuela Lacana, Ph.D., Associate Chief Lab. of Chemistry 7/17/09
Gibbes Johnson, Ph.D., Chief Lab. of Chemistry
Barry Cherney, Ph.D., Deputy Director DTP 7-17-09
Amy Rosenberg, M.D. PhD. Director, DTP

SUBJECT: Quality Review of STN 125293 Drug Product, Original Submission
Pegylated Modified Porcine Uricase

CDER RECEIPT DATE: 31 October 2008
MID CYCLE DATE: 31 January 2009
PUDFA DATE: 31 April 2009
PUDFA DATE EXTENSION: 31 July 2009

SPONSOR: Savient Pharmaceuticals, Inc. (Savient)
One Tower Center, 14th Floor
East Brunswick, NJ 00816

DRUG PRODUCT MANUFACTURER: Enzon Pharmaceuticals, Inc
6925 Guion Road
Indianapolis, IN 46268
USA

DRUG SUBSTANCE: Reviewed by Howard Anderson, Ph.D, Biologist, DTP
INDICATION: Treatment Resistant Gout
CLINICAL BRANCH: Division of Anesthesia, Analgesia and Rheumatology Products
RPM: Diana Walker, Ph.D

DMF LOA Provided: (b) (4)

ADMINISTRATIVE:

This application involves puricase, a clear colorless, sterile solution containing 8 mg/ml of uricase protein conjugated to methoxypolyethylene glycol (mPEG) in phosphate buffered saline. Savient has requested a categorical exclusion from an environmental assessment. The expected introduction concentration of the active moiety into the aquatic environment will be (b) (4). Under 21 CFR Section 25.31(b) Puricase meets the criteria for a categorical exclusion regarding an action on this BLA since the active moiety estimated concentration at the point of entry into the aquatic environment will be below 1 part per billion. I therefore recommend approval of this request.

The drug product section of the review was written by Richard Ledwidge. During the review, deficiencies were identified that required additional information from the sponsor. An information request was sent to the sponsor on May 28, 2009. The sponsor provided responses on June 11, 2009. A second information request was sent to the sponsor on June 26, 2009. The sponsor provided responses on July 10, 2009. Both of the sponsor's responses are included in the review.

RECOMMENDATION: Complete Response

The following issues need to be addressed by Savient for complete review of the CMC section of the BLA. Provided below are issues identified during the primary quality product review. The most significant issue is item number 1 that deals with comparability of phase III and commercial product.

Complete Response Issues (<u>Finalized CR comments are included in the Executive Summary</u>)

(b) (4)

Please include a true identity assay such as N-terminal sequencing or ELISA with an appropriate product specific antibody.

3) The proposed release tests for purity are inadequate to monitor protein degradation. Please include in your release a purity assay that monitors protein degradation.

4) Specifications for release need to reflect manufacturing history. In particular the specifications for kinetic parameters, (b) (4) *specific activity and* (b) (4) *levels are too broad and do not represent manufacturing capabilities.*

5) Please perform leachable/extractable studies on the commercial container closure system.

7) Please perform additional studies in infusion bags to ensure that product is stable during infusion.

8) Please include in your release testing an assay that characterizes pegylation site consistency.

9) Sponsor needs to provide validation studies on the transport of DS and DP.

92 Page(s) Withheld in Full immediately following this page as B4 (CCI/TS)

STN 125293 Product PEGLOTICASE

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
☒ Drug Substance	Y	N	
☐ Drug Product	Y	N	
☐ Facilities and Equipment	Y	N	
☒ Adventitious Agents Safety Evaluation	(Y)	N	
☐ Novel Excipients	Y	N	
☐ Executed Batch Records	Y	(N)	FDA INFORMED COMPANY BATCH TEMPLATE WOULD BE APPROP. PROVIDED, WILL CHECK EXECUTED LOTS ON INSPECTION
☒ Method Validation Package	(Y)	N	
☐ Comparability Protocols	Y	(N)	PHASE 3 SAME AS TO BE MARKETED

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	(Y)	N	
Drug Substance (API) [3.2.S]			
☐ general info	(Y)	N	
☒ nomenclature			
☒ structure (e.g. sequence, glycosylation sites)			
☒ properties			
☐ manufacturers	Y	N	
o facility name			
o full address (street, city, state, country)			
o is facility registered with FDA			
o FEI number			
☐ contact person	Y	N	
o full name and title			
o telephone			
o fax			
o email			
☐ Confirmation by applicant that each API facility, including contractors and subcontractors, understand their specific role in the manufacturing process as described in the application.	Y	N	
☐ Confirmation by written statement from each API facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.)	Y	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
☐ API processing product type: primary mode of deriving API	Y N	
☐ fermentation, bacterial host		
o fermentation, mammalian host		
o chemical synthesis		
o extraction/isolation, only		
☐ batch numbering and pooling scheme		
☐ cell culture and harvest		
☐ purification		
☐ filling, storage and shipping		
☐ description of manufacturing process	Y N	
☐ batch numbering and pooling scheme		
☐ cell culture and harvest		
☐ purification		
☐ filling, storage and shipping		
☐ control of materials	Y N	
☐ raw materials and reagents		
☐ biological source and starting materials		
☐ cell substrate: source, history, and generation		
☐ cell banking system, characterization, and testing		
☐ control of critical steps and intermediates	Y N	
☐ justification of specifications		→ ACCEPTANCE RANGES
o analytical method validation		
☐ reference standards		
☐ stability		
☐ process validation (prospective plan, results, analysis, and conclusions)	Y N	
☐ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
☐ characterization of drug substance	Y N	
☐ control of drug substance	Y N	
☐ specification		
☐ justification of specs.		
☐ analytical procedures		
☐ analytical method validation		
☐ batch analyses		
☐ consistency (3 consecutive lots)		

CTD Module 3 Contents	Present?	If not, justification, action & status
☒ justification of specs.		
☒ reference standards	(Y) N	
☒ container closure system	(Y) N	
☒ stability	(Y) N	
☒ summary		
☐ post-approval protocol and commitment		
☒ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P]		
☐ description and composition	(Y) N	
☐ pharmaceutical development	(Y) N	
☐ manufacturers	(Y) N	
o facility name		
o full address (street, city, state, country)		
o is facility registered with FDA		
o FEI number		
☐ contact person	Y (N)	
o full name and title		
o telephone		
o fax		
o email		
☐ Confirmation by the applicant that each facility, including contractors and subcontractors, understands their specific role in the manufacturing process as described in the application.	(Y) N	
☐ Confirmation by written statement from each facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.)	Y N	Facility was recently inspected. We will not be inspecting DP facility for this application
☐ batch formula	(Y) N	
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
☐ finished drug processing: mixing/homogenizing components	Y N	Not Applicable
o dry powder mixing		

CTD Module 3 Contents	Present?	If not, justification, action & status
o granulation, wet o granulation, dry o granulation high/low shear o micro fluidization o emulsification o milling/micronization o sieving/particle sizing o spray drying o fluidized bed drying o tray drying o mixing, suspension o mixing, liquids not solution/suspension		
❑ finished drug processing: forming dosing/delivery unit o compression (compaction of a powder, slug, or granules by a press; includes multilayer tablets prepared by more than one compression cycle.) o molding (Forming a solid dosage other than by compaction, as in making suppository, lozenge, pill, soap, softgel, and gum.) o fabrication, inhalers liquid and gas cold fill o fabrication, inhalers dry powder o fabrication, transdermals o fabrication, pre-filled syringe o filling, powder/granule o extrusion (other than as used in granulation) o coating, color/taste only o coating delay/extend o release rate (includes coating tablets as well as granules, beads, or pellets) ● filling, solution o filling suspension o filling, liquids not solution/suspension o filling, semi-solid	(Y) N	
❑ component and finished drug processing aseptic fill and sterilization ● aseptic filling, manual process (including liquid and solid filling)	(Y) N	

CTD Module 3 Contents	Present?		If not, justification, action & status
❑ aseptic filling, isolator process (enclosed environments for filling sterile drug, including blow-fill-seal, into which human intervention is not ❑ expected or intended during process) o terminal sterilization (by any method, including steam, gas, dry heat, water, and radiation)	(Y)	N	
❑ other operations o lyophilization o irradiation by cyclotron (positron emission tomography (PET) drugs o irradiation other (not intended to achieve sterility and not CYC) o not elsewhere classified (to be used infrequently and cautiously)	Y	N	Not Applicable
❑ finished drug processing: medical gas o gas separation (includes separation operations that also fill into vessels) o gas filling only	Y	N	Not applicable
❑ controls of critical steps and intermediates	(Y)	N	
❑ process validation including aseptic processing & sterility assurance: ❑ 3 <u>consecutive</u> lots o other needed validation data	(Y)	N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	(Y)	N	
❑ control of drug product (justification of specifications; analytical method validation)	(Y)	N	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	(Y)	N	
❑ stability ❑ summary	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation		
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent	Y N	No Diluent
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	 (b) (4)
Laboratory (Contractor) ❑ laboratories o facility name o full address (street, city, state, country) o FEI number	Y N	
❑ contact person o full name and title o telephone o Fax o email	Y N	
❑ Confirmation by applicant that each test facility, including contractors and subcontractors, understands their specific role in the testing process as described in the application.	Y N	
❑ Confirmation by written statement from each testing facility that they are ready for inspection, or the applicant identifies at what date the facility will be ready for inspection *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.)	Y N	
❑ Each testing facility identified in the application and identification of the type of testing performed by the facility (if more than one type of testing is performed by a single facility, identify each type of testing.) o finished dosage o API o QC released testing/stability finished dosage or both o chemistry o microbiological	Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	Y N	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production		
❑ novel excipients		
USA Regional Information [3.2.R]		
❑ executed batch records	Y (N)	TEMPLATE PROVIDED(DS)
❑ method validation package	(Y) N	
❑ comparability protocols	Y (N)	PHASE 3 SAME AS MARKETED(DS)
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?		
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	
❑ all electronic submission components usable	(Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
(including pilot facilities) using the final production process(es)?		
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y (N)	PHASE III SAME AS COMMERCIAL
certification that all facilities are ready for inspection	Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	(Y) N (Y) N (Y) N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval	Y (N)	Original submission

Examples of Filing Issues	Yes?	If not, justification, action & status
manufacturing changes, is animal or clinical data needed? Was it submitted?		

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

For Applications: Were any potential review issues identified for the day 74 letter? Yes (No)

Reviewer: Howard Anderson CMC REVIEWER DS 17 DEC 2008 Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

(Richard Ledwidge) CMC Reviewer DP 17/12/08

Concurrence:

Branch/Lab Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

12-17-08